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# A META-ANALYSIS OF LONG- VERSUS SHORT-ACTING PHOSPHODIESTERASE 5 INHIBITORS: COMPARING COMBINATION USE WITH A-BLOCKERS AND A-BLOCKER MONOTHERAPY FOR LOWER URINARY TRACT SYMPTOMS

Hypothesis / aims of study
Combination therapy with an α-1-adrenergic blocker and phosphodiesterase type 5 inhibitors (PDE5Is) has shown improvements in lower urinary tract symptoms (LUTS) with negligible side effects. Nonetheless, decisive advantages in symptom improvement were insufficient, and there were no clinical differences between long- or short-acting PDE5Is in combination with α-blockers and α-blocker monotherapy.

Study design, materials and methods
To review and meta-analyze studies on α-1 adrenergic blocker monotherapy and combination therapy with long- versus short-acting PDE5Is including a subanalysis of their use in LUTS. A search of the MEDLINE, Embase, Cochrane Library, and KoreaMed databases was conducted from 2000 to 2014 using combinations of the following terms: α-blockers, α-1-adrenergic blocker, LUTS, BPH, ED, and PDE5Is. Among the 323 relevant references discovered, 10 were selected for meta-analysis.

Results
Meta-analysis of the combination therapy showed it was more effective than α-blockers in improving symptoms, with a mean International Prostrate Symptom Score change difference of −1.93 while those of the long- versus short-acting PDE5I were −2.12 versus −1.70. Compared to maximum flow rate (Qmax) value with monotherapy, the Qmax increased more with the combination therapy (mean difference of 0.71) while change values were 0.14 and 1.13 for the long- and short-acting PDE5Is, respectively. Residual urine decreased more with the combination therapy than it did with α-1-adrenergic blocker monotherapy with a mean difference of −7.09 while the mean residual urine change values for long- versus short-acting PDE5Is were −18.83 versus −5.93.
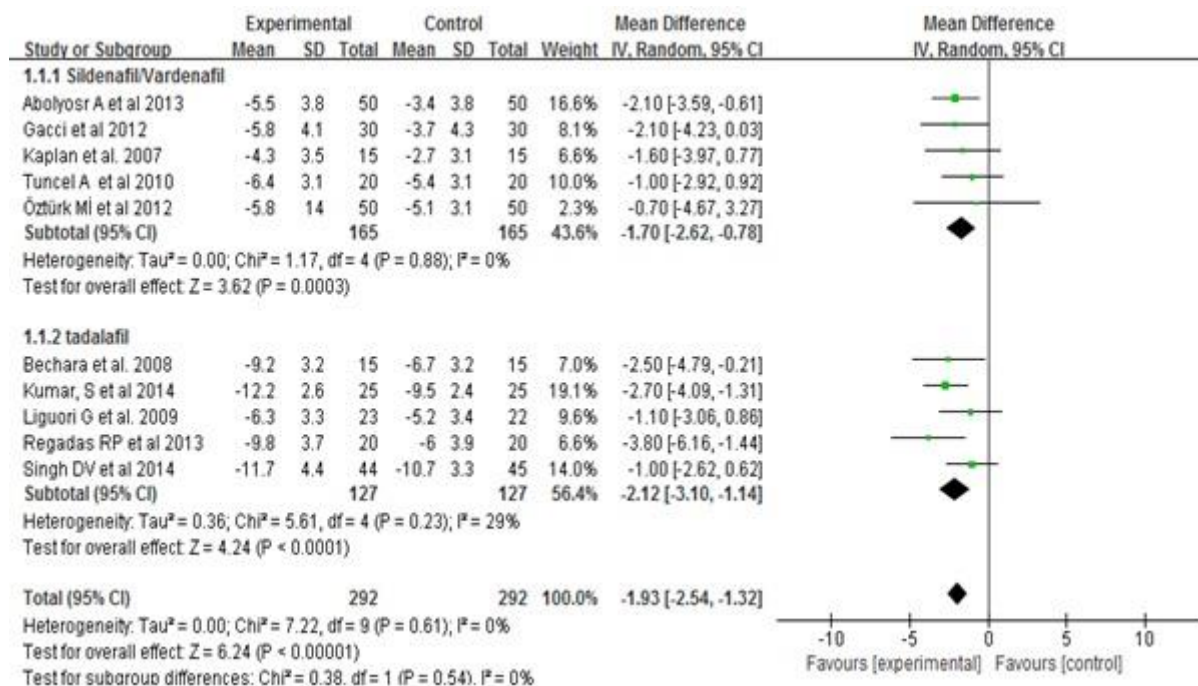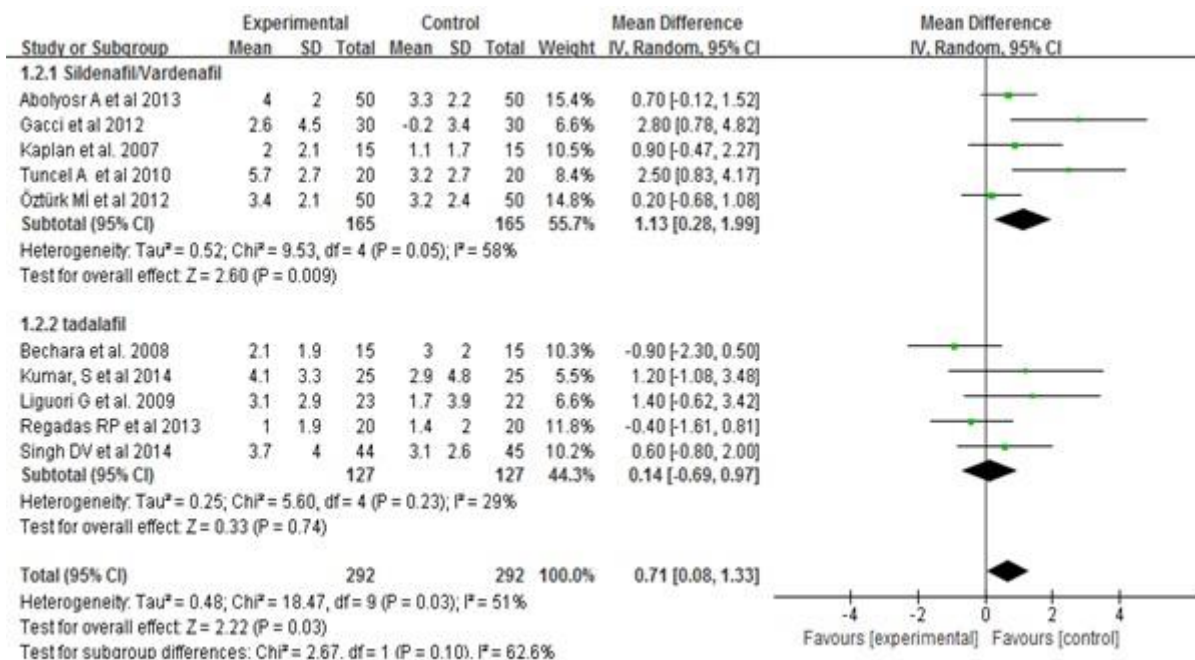
Interpretation of results
Our meta-analysis of the accessible studies suggests that PDE5Is can significantly improve LUTS in men with benign prostatic hyperplasia

Concluding message
combination PDE5I and α-1-adrenergic blocker therapy could be a more effective short-term treatment than α-1-adrenergic blocker monotherapy for patients with LUTS and ED, and the differences between long and short-acting agents were minimal.

Weighted differences (with 95% confidence interval [CI]) of International Prostate Symptom Score (IPSS) and maximum flow rate (Qmax) between PDE5Is plus a-blocker ( Experiment )versus a-blocker alone (control).



| Study or Subgroup | Experimental | | | Control | | | Weight | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Total | Mean | SD | Total | | | |
| **1.1.1 Sildenafil/Vardenafil** | | | | | | | | | |
| Abolyosr A et al 2013 | -5.5 | 3.8 | 50 | -3.4 | 3.8 | 50 | 16.6% | -2.10 [-3.59, -0.61] | |
| Gacci et al 2012 | -5.8 | 4.1 | 30 | -3.7 | 4.3 | 30 | 8.1% | -2.10 [-4.23, 0.03] | |
| Kaplan et al. 2007 | -4.3 | 3.5 | 15 | -2.7 | 3.1 | 15 | 6.6% | -1.60 [-3.97, 0.77] | |
| Tuncel A et al 2010 | -6.4 | 3.1 | 20 | -5.4 | 3.1 | 20 | 10.0% | -1.00 [-2.92, 0.92] | |
| Öztürk MI et al 2012 | -5.8 | 14 | 50 | -5.1 | 3.1 | 50 | 2.3% | -0.70 [-4.67, 3.27] | |
| Subtotal (95% CI) | | | 165 | | | 165 | 43.6% | -1.70 [-2.62, -0.78] | |
| Heterogeneity: Tau² = 0.00; Chi² = 1.17, df = 4 (P = 0.88); I² = 0% | | | | | | | | | |
| Test for overall effect: Z = 3.62 (P = 0.0003) | | | | | | | | | |
| **1.1.2 tadalafil** | | | | | | | | | |
| Bechara et al. 2008 | -9.2 | 3.2 | 15 | -6.7 | 3.2 | 15 | 7.0% | -2.50 [-4.79, -0.21] | |
| Kumar, S et al 2014 | -12.2 | 2.6 | 25 | -9.5 | 2.4 | 25 | 19.1% | -2.70 [-4.09, -1.31] | |
| Liguori G et al. 2009 | -6.3 | 3.3 | 23 | -5.2 | 3.4 | 22 | 9.6% | -1.10 [-3.06, 0.86] | |
| Regadas RP et al 2013 | -9.8 | 3.7 | 20 | -6 | 3.9 | 20 | 6.6% | -3.80 [-6.16, -1.44] | |
| Singh DV et al 2014 | -11.7 | 4.4 | 44 | -10.7 | 3.3 | 45 | 14.0% | -1.00 [-2.62, 0.62] | |
| Subtotal (95% CI) | | | 127 | | | 127 | 56.4% | -2.12 [-3.10, -1.14] | |
| Heterogeneity: Tau² = 0.36; Chi² = 5.61, df = 4 (P = 0.23); I² = 29% | | | | | | | | | |
| Test for overall effect: Z = 4.24 (P < 0.0001) | | | | | | | | | |
| Total (95% CI) | | | 292 | | | 292 | 100.0% | -1.93 [-2.54, -1.32] | |
| Heterogeneity: Tau² = 0.00; Chi² = 7.22, df = 9 (P = 0.61); I² = 0% | | | | | | | | | |
| Test for overall effect: Z = 6.24 (P < 0.00001) | | | | | | | | | |
| Test for subgroup differences: Chi² = 0.38, df = 1 (P = 0.54), I² = 0% | | | | | | | | | |

Favours [experimental]   Favours [control]

| Study or Subgroup | Experimental | | | Control | | | | Mean Difference | Mean Difference |
| | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|---|
| **1.2.1 Sildenafil/Vardenafil** | | | | | | | | | |
| Abolyosr A et al 2013 | 4 | 2 | 50 | 3.3 | 2.2 | 50 | 15.4% | 0.70 [-0.12, 1.52] | |
| Gacci et al 2012 | 2.6 | 4.5 | 30 | -0.2 | 3.4 | 30 | 6.6% | 2.80 [0.78, 4.82] | |
| Kaplan et al. 2007 | 2 | 2.1 | 15 | 1.1 | 1.7 | 15 | 10.5% | 0.90 [-0.47, 2.27] | |
| Tuncel A et al 2010 | 5.7 | 2.7 | 20 | 3.2 | 2.7 | 20 | 8.4% | 2.50 [0.83, 4.17] | |
| Öztürk MI et al 2012 | 3.4 | 2.1 | 50 | 3.2 | 2.4 | 50 | 14.8% | 0.20 [-0.68, 1.08] | |
| Subtotal (95% CI) | | | 165 | | | 165 | 55.7% | 1.13 [0.28, 1.99] | |

Heterogeneity: Tau² = 0.52; Chi² = 9.53, df = 4 (P = 0.05); I² = 58%
Test for overall effect: Z = 2.60 (P = 0.009)

| Study or Subgroup | Experimental | | | Control | | | | Mean Difference | Mean Difference |
| | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|---|
| **1.2.2 tadalafil** | | | | | | | | | |
| Bechara et al. 2008 | 2.1 | 1.9 | 15 | 3 | 2 | 15 | 10.3% | -0.90 [-2.30, 0.50] | |
| Kumar, S et al 2014 | 4.1 | 3.3 | 25 | 2.9 | 4.8 | 25 | 5.5% | 1.20 [-1.08, 3.48] | |
| Liguori G et al. 2009 | 3.1 | 2.9 | 23 | 1.7 | 3.9 | 22 | 6.6% | 1.40 [-0.62, 3.42] | |
| Regadas RP et al 2013 | 1 | 1.9 | 20 | 1.4 | 2 | 20 | 11.8% | -0.40 [-1.61, 0.81] | |
| Singh DV et al 2014 | 3.7 | 4 | 44 | 3.1 | 2.6 | 45 | 10.2% | 0.60 [-0.80, 2.00] | |
| Subtotal (95% CI) | | | 127 | | | 127 | 44.3% | 0.14 [-0.69, 0.97] | |

Heterogeneity: Tau² = 0.25; Chi² = 5.60, df = 4 (P = 0.23); I² = 29%
Test for overall effect: Z = 0.33 (P = 0.74)

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Total (95% CI) | | | 292 | | | 292 | 100.0% | 0.71 [0.08, 1.33] | |

Heterogeneity: Tau² = 0.48; Chi² = 18.47, df = 9 (P = 0.03); I² = 51%
Test for overall effect: Z = 2.22 (P = 0.03)
Test for subgroup differences: Chi² = 2.67, df = 1 (P = 0.10), I² = 62.6%

Favours [experimental]  Favours [control]

References
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